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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/589,102	10/05/2007	Tae-Yoon Kim	SIGONG-13046	5838

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Casimir Jones, S.C.
2275 DEMING WAY, SUITE 310
MIDDLETON, WI 53562

EXAMINER	
NOBLE, MARCIA STEPHENS	
ART UNIT	PAPER NUMBER
1632	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/589,102	KIM ET AL.	
	Examiner	Art Unit	
	MARCIA S. NOBLE	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *28 April 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10 August 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Withdrawn Rejections/Objections

The rejection of claims 1-15, under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, is withdrawn. A scope of enablement rejection was on three grounds. First the breadth of the claims 1 and its dependent encompassed a method with no result. Applicant amended claim 1 to add a result step that overcomes this enablement issue. Second, the breadth of all the claims encompasses administering an ODN without the requirement that the ODN be expressed. Applicant asserts in the remarks that expression of the ODN is not needed because the CpG ODN is the active form of reagent. Applicant's argument is found persuasive and therefore this issue of enablement is overcome. Third, the breadth of the claims was not enabled because they recite administering the CpD ODN to a subject without the requirement that the ODN be delivered to the site of inflammatory skin disease. Applicant provides a Declaration from one of the inventors to address this issue of enablement.

The declaration under 37 CFR 1.132, filed 4/28/2010, is sufficient to overcome the rejection of claims 1-15 based upon 112, 1st paragraph enablement rejection. The declaration provides evidence that intravenous delivery of a CpG ODN of the instant invention is effective in treating atopic dermatitis in a skin hyperimmune response model, wherein atopic dermatitis is induced by ovalbumin administration (sections 1 and 2). The declaration also provides evidence that intraperitoneal delivery of a CpG ODN of the instant invention is effective in treating atopic dermatitis in the skin hyperimmune

response model (sections 3 and 4). This evidence, in addition to the effective treatment of atopic dermatitis using a topical delivery of a CpG ODN of the instant invention taught by the specification, demonstrates that the administration of the CpG ODN to a subject should treat an inflammatory skin disease, as claimed, with a reasonable expectation of success. Thus, the declaration is sufficient to overcome the third issue of enable. Thus, because Applicant has addressed and overcome all of the issues of enablement, the rejection is withdrawn.

The objection to claim 17, under 37 CFR 1.75 as being a substantial duplicate of claim 16, is withdrawn. Applicant canceled claim 17.

Upon additional search and consideration, the following rejection is needed:

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the following:

A) A method for inhibiting a Th2 cytokine and inducing a Th1 cytokine, comprising administering to a subject in need thereof an effective amount of the isolated CpG ODN of SEQ ID NO:2, wherein said administering results in inhibition of a Th2 cytokine and induction of a Th1 cytokine is said subject;

B) A method of treating atopic dermatitis associated with increased Th2 cytokines, increased Th1 cytokines, and elevated IgE serum levels in a subject comprising administering said subject an effective amount of the isolated CpG ODN of SEQ ID NO:2, wherein said administering is correlated with improvement of said atopic dermatitis in said subject; and

C) A composition for treating atopic dermatitis associated with atopic dermatitis associated with increased Th2 cytokines, decreased Th1 cytokines, and increased IgE serum levels comprising the isolated CpG ODN of SEQ ID NO:2, does not reasonably provide enablement for the following:

1) A method for inhibiting a Th2 cytokine or inducing a Th1 cytokine; 2) a method of stimulating any immune response other than one that inhibits a Th2 cytokine and induces a Th1 cytokine; 3) A method of treating a inflammatory skin disease that administers any other CpG ODN other than SEQ ID NO:2; and 4) A composition for preventing an inflammatory skin disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would require undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the

invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make and use the invention based on the content of the disclosure is "undue".

Claim 11 and it dependents are drawn to a method of treating an inflammatory skin disease using the generic sequence of SEQ ID NO:1. Claim 16 is drawn to a composition comprising the generic SEQ ID NO:1 for treating an inflammatory skin disease.

The specification teaches that although the etiology of atopic dermatitis is not defined up to date, it is thought that allergen-specific T cell that product Th2 cytokines including IL-4 and IL-5 cause atopic dermatitis. Further, it is reported that patients with atopic dermatitis have reduced Il-12 production and increased serum IgE. The specification further teaches that an CpG ODN therapy that increases dendritic IL-12 production and decreases Th2 cytokines is expected to be an effective treatment for atopic dermatitis (p. 42, lines 2-17). In working Example 5, the specification teaches the topic application of the CpG ODN of SEQ ID NO:2 to skin lesion in NC/Nga mice, an animal model for atopic dermatitis (p. 33, line 23 to p. 34, line 2). On days 5 and 7 following the topic application, lesions in mice that received the CpG ODN disappeared; while lesions in mice that did not received the CpG ODN persisted (p. 34, lines 5-11). Under histological analysis of the site of the lesions, the lesion sites of mice that received the CpG ODN showed significantly less hyperkeratosis and acanthosis, as well decreased infiltration of lymphocytes in the dermis compared to controls. Thus, the

specification teaches that that CpG ODN effectively treats atopic dermatitis skin lesions (p. 34, lines 11-15). The specification further teaches that the topic application of the CpG ODN significantly decreased the Th2 cytokines, IL-4 and IL-10 and significantly increased the Th1 cytokine in the epidermis of the treated mice (p. 35, lines 11-21). Further the specification teaches that the topic application of the CpD ODN significantly decreased serum IgE levels in the blood of treated mice (p. 37, lines 14-16). Therefore, the specification provides specification guidance to teach one specific CpD ODN, SEQ ID NO:2, that effectively treats atopic dermatitis that is associated with increased Th2 cytokines, decreased Th1 cytokines, and increased IgE serum levels.

However, the claims are more broadly drawn to the use of a generic CpG ODN encoded by the formulate of SEQ ID NO:1. SEQ ID NO:2 is a species encompassed by SEQ ID NO:1, but SEQ ID NO:1 encompasses many more variants than SEQ ID NO:2 and the specification fails to provide specific guidance to teach that these other variants encompassed by SEQ ID NO:1 are capable of treating an inflammatory skin disease as claimed.

At the time of the invention, Hussain (Hussain and Kline. J Invest Dermatol Symp Proc 9:23-28, 2004) teaches CpG ODNs contain DNA motifs centered around an unmethylated CG dinucleotide that have immunostimulatory effects in mammals similar to those of native bacterial DNA (p. 25, col 2, lines 4-6). Hussain teaches that topical administration on bare skin of CpG ODN present in influenza peptide and cholera toxin coding sequences induce a shift from Th2 cytokines to expressing Th1 cytokines, with an increase in IFN gamma and a decrease in IL-4, as well as a decrease in total serum

IgE levels (p. 27, col 1, 1st full par, lines 17-24). Hussain further contemplates given that status of the art, CpG ODN may be attractive therapy in the treatment of acute atopic dermatitis (p. 27, col 1, 1st full par, lines 24-27). Thus, from status of the art suggests that CpG ODN are effective in stimulating immune response, and more particularly effective in inhibiting Th2 cytokines and inducing a Th1 cytokine in vivo. The state of the art further contemplates the use of CpG ODNs for treatment of inflammatory skin diseases, such as acute atopic dermatitis.

However, the breadth of "an inflammatory skin disease" encompasses chronic atopic dermatitis and Hussain teaches chronic atopic dermatitis has significantly lower Th2 cytokines and express higher levels of Th1 cytokines. Thus the effectiveness of CpG ODN treatment on chronic atopic dermatitis is speculative, and thus unpredictable (p. 27, 1st full par, lines 27-32). Therefore, the art of Hussain suggest that CpG ODN treatment will not predictably treat all inflammatory skin disease, more particularly not all atopic dermatitis forms. Tokura (J Dermatol Sci 58:1-7, 2010) teaches that atopic dermatitis can be categorized into extrinsic and intrinsic type (see p. 1, abstract, line 1). Tokura teaches that the intrinsic form is an inflammatory skin disease associated with low levels of Th2 cytokines, elevated Th1 cytokines (p. 4, col 2, section 6.1, par 1, lines 5-11). Therefore, a treatment such as CpG ODN that reduces Th2 cytokines and increases Th1 cytokines would not predictably treat intrinsic atopic dermatitis.

The breadth of “an inflammatory skin disease” also encompasses skin cancer because often encompasses inflammation response, albeit ineffective ones. As previously made of record, Najar and Dutz (J Invest Derm 128:2204-2210, 2008) teach

that administration of CpG to skin tumors in mice were not able to prevent skin cancer or mortality associated with skin cancer (p. 2205, col 2, Figure 1a and b). Therefore, Nahar and Dutz teach that administration of a CpG ODN will not predictably treat the inflammatory skin disease of skin caner.

Further, the art further teaches that not all CpG ODNs are equivalent in their ability to generate immune responses. Ballas (Ballas et al. J Immunol 167:4878-4886, 2001) teaches that treatment or prevention of melanoma with CpG ODNs was variable depending upon the variant of the CpG ODN sequence used (p. 4878, col 2, last par, p. 4879, table 1, p. 4881, col 1 and figure 4). Therefore, the art of Ballas teaches that not all variant of will effectively and predictably treat an inflammatory skin disease as claimed.

Therefore, the breadth of the instant claims encompassing treating any skin inflammation using any CpG ODN variant of SEQ ID NO:1 other than SEQ ID NO:2 is not enabled. The specification narrowly teaches a treatment of atopic dermatitis associated with increased levels of Th2 cytokines, decreased levels of Th1 cytokines, and increased serum IgE that is effectively treated with SEQ ID NO:2. In contrast, the specification fails to teach the broader embodiments encompassed by the treatment of any inflammatory skin disease with any variant of SEQ ID NO:1. Further, the art teaches that not all CpG will predictably treat a skin disease or stimulate an immune response and not all inflammatory skin diseases will be treated by the CpG ODNs.

Claim 1 and its dependents recites, "a method for inhibiting a Th2 cytokine and/or inducing a Th1 cytokine".

As discussed above, the specification provides specific guidance to a SEQ ID NO:2 the elicit both an inhibition in Th2 cytokine and an induction of a Th1 cytokine. The specification fails to teach a method that inhibits a Th2 cytokine only or a Th1 cytokine only. Further Hussain teaches Th1 and Th2 cell interact in a counter-regulatory fashion, maintaining a critical balance (p. 23, col 1, last par, lines 1-2). Further, Hussain teaches that treatments that solely increase Th1 cytokines fail to significantly treat inflammations associated with lowered Th1 cytokines but further cause significant adverse reactions associated with disrupting the TH1/Th2 cytokine balance (p. 23, abstract). Therefore, the art teaches that a method that inhibits Th2 cytokine or induces Th1 cytokine as the breadth of claim 1 and its dependents encompasses will not predictably occur with the treatment of the ODN of the instant invention. The specification teaches a method that inhibits Th2 cytokines and induces a Th1 cytokine. Thus, this is the embodiment enabled by the specification.

Claim 1 and its dependents are being scoped to SEQ ID NO:2 as well because the claim recites "a subject in need thereof". This recitation implies a treatment method because the only subjects in need thereof are one that require a therapeutic effect. As discussed above SEQ ID NO:2 is the only ODN that has been predictably demonstrated to have a therapeutic effect on a subject in need thereof as claimed.

Claim 7 and its dependents recite, "a method of stimulating an immune response...in a subject in need thereof". The broadest method claim is drawn to stimulating an immune response. The art teaches that an "immune response" is any of the body's immunologic reactions to an antigen (See Immune Response definition

printout from http://dictionary.reference.com/browse/immune+response, printed out 7/28/2010, page 1.) Therefore the breadth of an immune response is quite broad encompassing any immunological event. The method and composition claims are also drawn to treating an inflammatory skin disease which can encompass any skin irritation or inflammation brought about my any means. However, the specification fails to teach any other immune response other than one that inhibits TH2 cytokines and induces TH1 cytokines.

Claim 7 and its dependents are being scoped to SEQ ID NO:2 as well because the claim recites "a subject in need thereof". This recitation implies a treatment method because the only subjects in need thereof are one that require a therapeutic effect. As discussed above SEQ ID NO:2 is the only ODN that has been predictably demonstrated to have a therapeutic effect on a subject in need thereof as claimed.

Thus, in summary, the full breath of the claims has been deemed to lack enablement. The specification narrowly provides specific guidance to a therapeutic method and composition for the treatment of atopic dermatitis associated with increased Th2 cytokines and decreased cytokines that functions by administering SEQ ID NO:2 which has the specific result of inhibiting Th2 cytokines and increasing Th1 cytokines which result in treatment of the atopic dermatitis. The art teaches that not all CpG ODN will elicit predictably elicit an immune response, inhibit Th2 cytokines, increase Th1 cytokines, and treat all types of inflammatory diseases. Thus, the claimed invention is scoped to the predictable teachings of the invention by the specification.

Therefore at the time of filing the skilled artisan would need to perform an undue amount of experimentation without a predictable degree of success to implement the invention as claimed.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MARCIA S. NOBLE whose telephone number is (571)272-5545. The examiner can normally be reached on M-F 9 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Marcia S. Noble, PhD
AU 1632

/Thaian N. Ton/
Primary Examiner, Art Unit 1632